World Journal of Gastrointestinal Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4251/wjgo.v7.i12.401

*World J Gastrointest Oncol* 2015 December 15; 7(12): 401-410
ISSN 1948-5204 (online)


REVIEW

# Targeted therapy for advanced gastric cancer: A review of current status and future prospects

Ozkan Kanat, Bert O'Neil, Safi Shahda

Ozkan Kanat, Department of Medical Oncology, Uludag University faculty of Medicine, 16059 Bursa, Turkey

Bert O'Neil, Safi Shahda, Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN 46202, United States

Author contributions: All authors contributed equally to writing this review.

Conflict-of-interest statement: Authors declare no conflict of interest for this article.



Correspondence to: Ozkan Kanat, MD, PhD, Professor, Department of Medical Oncology, Uludag University faculty of Medicine, McIntyre Medical Building, 3655 Sir William Osler Montreal, Quebec H3G1Y6, 16059 Bursa, Turkey. ozkanat@uludag.edu.tr
Telephone: +90-22-42951321

Received: May 21, 2015
Peer-review started: May 22, 2015
First decision: July 1, 2015
Revised: September 18, 2015
Accepted: October 23, 2015
Article in press: October 27, 2015
Published online: December 15, 2015

## Abstract

In the West in particular, the vast majority of gastric cancer (GC) patients present with advanced-stage disease. Although combination chemotherapy is still the most important component of treatment for these patients, it confers a modest survival advantage. Recently, increased knowledge of the key molecular signaling pathways involved in gastric carcinogenesis has led to the discovery of specific molecular-targeted therapeutic agents. Some of these agents such as trastuzumab and ramucirumab have changed the treatment paradigm for this disease. In this paper, we will summarize the current clinical status of targeted drug therapy in the management of GC.

**Key words:** Gastric cancer; Targeted therapy; Angiogenesis; Epidermal growth factor; Treatment



**Core tip:** Systemic chemotherapy confers a modest survival advantage in patients with advanced gastric cancer. The new therapeutic agents that target various inter- and intracellular signaling transduction pathways offer the promise of improved clinical outcomes in selected patients. The success of some of these agents has changed the treatment paradigm for advanced gastric cancer. We herein discuss the current and potential future roles of targeted therapy in the management of this malignancy.

Kanat O, O'Neil B, Shahda S. Targeted therapy for advanced gastric cancer: A review of current status and future prospects. *World J Gastrointest Oncol* 2015; 7(12): 401-410 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i12/401.htm
DOI: http://dx.doi.org/10.4251/wjgo.v7.i12.401

## INTRODUCTION

Gastric cancer (GC) is a very aggressive tumor and is currently the third leading cause of cancer-related deaths in both sexes at the world level (8.8% of the

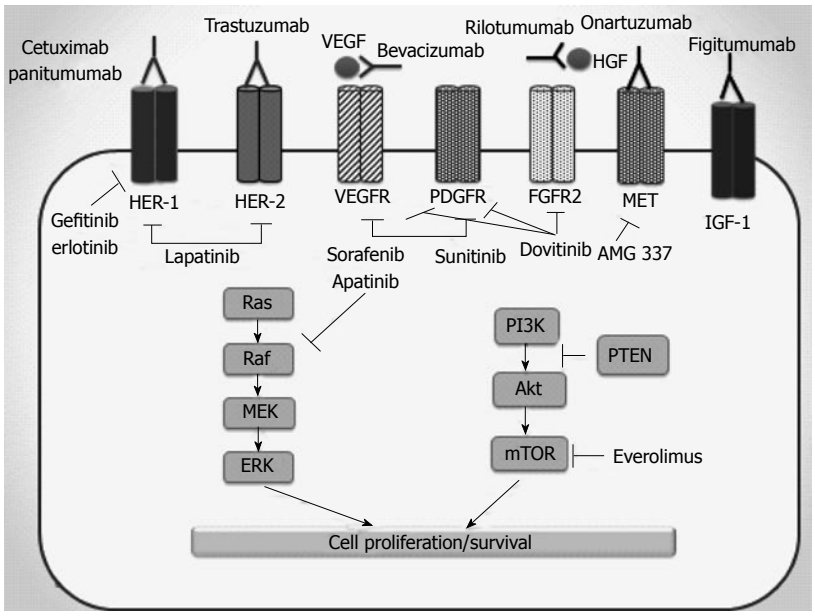


**Figure 1 Molecular targets and relevant drugs in metastatic gastric cancer.** HER: Human epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; HGF: Hepatocyte growth factor; FGFR2: Fibroblast growth factor receptor 2; IGF-1: Insulin-like growth factor 1; Raf: GTPase Raf; Ras: GTPase Ras; MEK: MAP kinase; ERK: Extracellular-signal-regulated kinase; PI3K: Phosphatidylinositol 3-kinase; PTEN: Phosphatase and tensin homolog; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin.

total)[1,2]. At initial diagnosis, a significant proportion of Western GC patients (65%) are found to have unresectable disease or distant metastases. In Japan and South Korea, where nationwide government-sponsored screening programs have been established, still up to 80% of patients who undergo a curative resection for GC develop locoregional or distant recurrence[2,3].

The clinical management of patients with advanced GC remains one of the most challenging tasks in clinical oncology. Until recently, systemic chemotherapy alone has been the mainstay of treatment for these patients[4]. However, the disease often exhibits relative resistance to chemotherapeutic agents, and a satisfactory response is achieved only in a minority of the patients[5,6]. In addition, although systemic chemotherapy can substantially increase symptom control and improve the patient's quality of life, its long-term results are still not satisfactory and unfortunately many patients die less than a year after starting therapy[5,6].

Thus, there is undoubtedly a need to develop more effective treatment strategies for this formidable disease. As in other solid tumors, the uses of targeted agents that block vital inter- and intracellular signaling pathways have recently emerged as a strategy for the treatment of advanced GC[7-12]. Significant advances in our understanding of the underlying biologic processes of GC have recently expanded the number and range of potential therapeutic targets. Targeted agents may be used either alone or in combination with anti-neoplastic agents for patients with both chemotherapy-naïve and chemotherapy-refractory disease. Some of these, such as trastuzumab and ramucirumab have been shown to have significant therapeutic activity and a good safety profile, have changed the treatment paradigm, and are therefore currently licensed in the United States and Europe as part of the management of patients with GC.

In this review, we will outline well-established targeted treatments for GC and discuss novel agents currently in development as well as some directions for future research.

### *Anti-epidermal growth factor receptor therapies*

The epidermal growth factor receptor (EGFR) belongs to the ErbB family of receptor tyrosine kinases (RTK), which contains four closely related members: ErbB1 (HER1 or EGFR), ErbB2 (Her2/neu), ErbB3 and ErbB4[13,14]. EGFR activation by one of its ligands initiates diverse downstream signaling pathways including the RAS/RAF/MAP kinase and PI3K/Akt/mTOR signaling networks. Both pathways play a vital role in several critical cellular processes including proliferation, growth, survival, motility, and tissue invasion[13,14].

EGFR overexpression has been correlated with more aggressive tumor behavior and a worse clinical results in patients with GC, suggesting that EGFR is therapeutic target for this aggressive malignancy[13,14]. The current therapeutic strategies targeting EGFR include neutralizing monoclonal antibodies (moAbs) directed against the extracellular receptor domain and small molecule tyrosine kinase inhibitors (TKIs) of the intracellular tyrosine kinase domain (Figure 1).

Cetuximab and panitumumab are engineered antibodies that bind to EGFR with higher affinity compared to its natural ligands[15,16]. Several phase II clinical trials have tested the feasibility of adding cetuximab to different chemotherapy regimens including 5-FU/folinic acid (LV)/irinotecan, 5-FU/LV/oxaliplatin (FOLFOX), docetaxel/cisplatin, capecitabine/cisplatin,

**Table 1 Summary of completed phase III trials of targeted agents in the treatment of advanced gastric and gastroesophageal adenocarcinoma**

| Author/trial | Line of treatment | Target | Agent | Treatment | ORR (%) | PFS (mo) | OS (mo) |
|---|---|---|---|---|---|---|---|
| Lordick *et al*[22] (2013)/ EXPAND | First | EGFR | Cetuximab | Cisplatin/capecitabine ± cetuximab | 30 *vs* 29 *P* = 0.77 | 4.4 *vs* 5.6 *P* = 0.32 | 9.4 *vs* 10.7 *P* = 0.95 |
| Waddell *et al*[23] (2013)/REAL-3 | First | EGFR | Panitumumab | EOX ± panitumumab | 46 *vs* 42 *P* = 0.42 | 6.0 *vs* 7.4 *P* = 0.068 | 8.8 *vs* 11.3 *P* = 0.013 |
| Bang *et al*[32] (2010)/ ToGA | First | HER2 | Trastuzumab | Cisplatin/capecitabine or 5-FU ± trastuzumab | 47 *vs* 35 *P* = 0.0017 | 6.7 *vs* 5.5 *P* = 0.0002 | 13.8 *vs* 11.1 *P* = 0.0046 |
| Hecht *et al*[34] (2013)/ LoGIC | First | EGFR/ HER2 | Lapatinib | CAPOX ± lapatinib | 53 *vs* 40 *P* = NA | 6.0 *vs* 5.4 *P* = 0.1 | 12.2 *vs* 10.5 *P* = 0.35 |
| Ohtsu *et al*[37] (2011)/ AVAGAST | First | VEGF-A | Bevacizumab | Cisplatin/capecitabine ± bevacizumab | 46 *vs* 37.4 *P* = 0.03 | 6.7 *vs* 5.3 *P* = 0.037 | 12.1 *vs* 10.1 *P* = 0.1002 |
| Shen *et al*[39] (2015)/ AVATAR | First | VEGF-A | Bevacizumab | Cisplatin/capecitabine ± bevacizumab | 40.7 *vs* 33.7 *P* = 0.348 | 6.3 *vs* 6.0 *P* = 0.47 | 11.4 *vs* 10.5 *P* = 0.55 |
| Bang *et al*[35] (2014)/TyTAN | Second | EGFR/ HER2 | Lapatinib | Paclitaxel ± lapatinib | 27 *vs* 9 *P* < 0.001 | 5.4 *vs* 4.4 *P* = 0.13 | 11.0 *vs* 8.9 *P* = 0.1044 |
| Fuchs *et al*[41] (2014)/ REGARD | Second | VEGFR-2 | Ramucirumab | BSC + ramucirumab or placebo | 3.4 *vs* 2.6 *P* = 0.76 | 2.1 *vs* 1.3 *P* < 0.0001 | 5.2 *vs* 3.8 *P* = 0.0473 |
| Wilke *et al*[43] (2014)/ RAINBOW | Second | VEGFR-2 | Ramucirumab | Paclitaxel + ramucirumab or placebo | 28 *vs* 16 *P* = 0.0001 | 4.4 *vs* 2.9 *P* < 0.0001 | 9.6 *vs* 7.4 *P* = 0.017 |
| Ohtsu *et al*[52] (2013)/ GRANITE-1 | Second or third | mTOR | Everolimus | Everolimus or placebo | 4.5 *vs* 2.1 *P* = NA | 1.7 *vs* 1.4 *P* < 0.001 | 5.4 *vs* 4.3 *P* = 0.124 |

ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival; EGFR: Epidermal growth factor receptor; EOX: Epirubicin, oxaliplatin and capecitabine; HER2: Human epidermal growth factor receptor 2; 5-FU: 5-fluorouracil; CAPOX: Capecitabine and oxaliplatin; NA: Not available; VEGF-A: Vascular endothelial growth factor A; VEGFR-2: Vascular endothelial growth factor receptor 2; mTOR: Mammalian target of rapamycin.

and capecitabine/oxaliplatin for chemotherapy-naïve advanced GC patients[17-20]. In these trials, overall response rates ranged from 41% to 69%, median progression-free survival (PFS) varied from 5 to 8.5 mo, and median overall survival (OS) varied from 9 to 16.6 mo. A randomized phase II clinical study (CALGB 80403/ ECOG 1206) evaluated three different conventional chemotherapy regimens (Epirubicin, cisplatin and 5-FU *vs* irinotecan and cisplatin *vs* FOLFOX) in combination with cetuximab. Response rates were 58%, 38%, and 51%, respectively, and median OS was 8.6 and 10 mo, respectively. Cetuximab combined with FOLFOX was found to be the least toxic of the three[21].

Unfortunately, these promising initial outcomes were not verified in the phase III EXPAND trial[22]. In this study, 904 previously untreated metastatic GC and gastro-esophageal junction (GEJ) cancer patients were randomly allocated to receive chemotherapy (cisplatin and capecitabine) with or without cetuximab[22]. No differences in clinical outcome were found between treatment groups, and the primary and secondary efficacy endpoints were not met; the median PFS and OS were 4.4 mo (95%CI: 4.2 to 5.5 mo) and 9.4 mo (95%CI: 8.3 to 10.6 mo), respectively in the combined therapy group compared with 5.6 mo (95%CI: 5.1 to 5.7 mo) and 10.7 mo (95%CI: 9.4 to 11.3 mo), respectively in the chemotherapy-alone group ($P$ = 0.32 and $P$ = 0.95 for PFS and OS, respectively). The addition of cetuximab also did not increase the overall response rate, which was 30% and 29% with or without cetuximab, respectively (Table 1).

Similarly, the phase III REAL-3 trial was performed to determine the effects of adding panitumumab to a combination chemotherapy regimen of epirubicin, oxaliplatin, and capecitabine (EOX) in patients with advanced esophago-gastric adenocarcinoma[23]. In this trial, patients were randomly allocated to receive EOX or a modified EOX plus panitumumab. Disappointingly, adding panitumumab to EOX chemotherapy resulted in worsened OS [8.8 mo compared with 11.3 mo for the EOX regimen (HR = 1.37; $P$ = 0.013)]. A trend toward a shorter PFS was also seen in patients receiving panitumumab (6.0 mo *vs* 7.4 mo, HR = 1.22; $P$ = 0.068). The panitumumab-containing arm was associated with an increased rate of grade 3-4 diarrhea (17% *vs* 11%), rash (11% *vs* 1%), mucositis (5% *vs* none), and hypomagnesaemia (5% *vs* none) but reduced rate of neutropenia (13% *vs* 28%).

Lastly, other novel humanized IgG1 anti-EGFR moAbs including matuzumab and nimotuzumab have also been investigated as first- or second-line treatment for advanced GC, and have also failed to generate a strong efficacy signal[24-26]. The small molecule EGFR TKIs have not been extensively studied in the treatment of advanced GC largely due to their limited activity in this setting[27,28]. Why EGFR-targeting strategies have failed to be successful in this disease in spite of lack of activating KRAS mutations and in spite of good biologic rationale remains a mystery.

### *Anti-HER2 (ERBB2) therapy*

As previously mentioned HER2 is another member of the ERB family of receptor tyrosine kinases[29]. Overexpression and amplification of the HER2 is detected in 10%-38% of GC patients[30]. Although the association between HER2 status and prognosis

in GC still controversial, the results of some clinical studies have suggested that patients with HER2 negative disease have a more favorable prognosis than those with HER2 positive disease[29,31]. Perhaps one of the most convincing data supporting the clinical benefits of targeted therapy in advanced GC come from the phase Ⅲ ToGA study[32]. This landmark study investigated the addition of trastuzumab, a moAb that binds to the extracellular ligand binding domain of the HER2 receptor, to combination chemotherapy (cisplatin and either capecitabine or 5-FU) in patients with previously untreated HER2 overexpressing [defined as HER2 fluorescence in situ hybridization (FISH) positive or immunohistochemistry (IHC) 3 positive], and advanced gastric or GEJ cancer. Over 3000 patients were screened for the study. Among the 594 enrolled patients, 296 received chemotherapy alone and 298 received chemotherapy plus trastuzumab. Patients receiving the combined therapy achieved improvement in all measures of efficacy including OS (13.8 mo *vs* 11.1 mo; HR = 0.74, *P* = 0.0046), PFS (6.7 mo *vs* 5.5 mo; HR = 0.71, *P* = 0.0002), and overall response rate (47% *vs* 35%, *P* = 0.0017). A post hoc subgroup analysis of the study demonstrated that the patients with strongly HER-2 positive tumors (defined as IHC2+/FISH+ or IHC3+) derived significant OS benefit from the addition of trastuzumab to chemotherapy (16 mo *vs* 11.8 mo, HR = 0.68). Moreover, the tolerability of the combination was good and there was no significant difference in the incidence of grade 3 or 4 side effects between the treatment groups. Based on these results, trastuzumab was approved in the Unites States and European Union for use in the first-line treatment of HER2-overexpressing locally advanced or metastatic GC.

Pertuzumab is a new moAb that binds to the extracellular ligand binding domain of HER2 and blocks its dimerization with other HER-family receptors[31]. When used together, the combination of pertuzumab plus trastuzumab provide a more comprehensive blockade of HER signalling than either agent alone. Therefore, the JACOB phase Ⅲ study is currently recruiting participants to evaluate the effectiveness of pertuzumab in addition to trastuzumab plus chemotherapy (cisplatin plus capecitabine or 5-FU) in chemo-naïve patients with HER2-overexpressing advanced gastric or GEJ cancer (NCT01774786).

Trastuzumab emtansine (T-DM1) is a newly developed HER2-targeted antibody–drug conjugate that links trastuzumab to a highly potent maytansine-derived anti-microtubule drug (DM1)[33]. After binding the trastuzumab moiety to HER2 receptors on the tumor surface, T-DM1 is internalized by endocytosis and degraded in lysosomes, resulting in release of DM1-containing cytotoxic catabolites[33]. A phase Ⅱ-Ⅲ trial (NCT01641939) is now investigating the effectiveness of T-DM1 compared with taxanes (docetaxel or paclitaxel) in patients with metastatic HER2-positive GC who develop progression of disease following first-line chemotherapy.

Lapatinib is an oral small-molecule tyrosine kinase inhibitor of EGFR and HER2 that blocks their tyrosine kinase activities. Two phase Ⅲ trials were performed to explore the effectiveness of lapatinib in first- and second-line treatment of advanced GC. The LoGIC Ⅲ trial investigated the efficacy of lapatinib when administered in combination with capecitabine plus oxaliplatin (CAPOX) as first-line therapy[34]. In total, 545 patients whose tumors overexpressed HER-2 were assigned to receive CAPOX plus lapatinib or placebo. No significant difference in survival between the two treatment arms was detected. Median OS and PFS in the chemotherapy + lapatinib group were 12.2 and 6 mo, respectively, compared to 10.5 and 5.4 mo in the control group. Similarly, in the phase Ⅲ TyTan trial conducted in Asia, 430 patients with advanced GC who had experienced failure of fluoropyrimidine and cisplatin-based chemotherapy and exhibited FISH-confirmed HER2 amplification received lapatinib plus weekly paclitaxel or weekly paclitaxel alone[35]. Although, the addition of lapatinib to paclitaxel extended the primary endpoint of OS from a median of 8.9 mo to 11.0 mo, this improvement failed to reach statistical significance (*P* = 0.1044). The further subgroup analysis revealed a statistically significant benefit in both OS and PFS from the addition of lapatinib to chemotherapy in patients with HER2 IHC3+ tumors and in Chinese patients.

### *Targeting angiogenesis pathways*

Angiogenesis is necessary for tumors to grow beyond a certain size, survive or spread. Vascular endothelial growth factor (VEGF) and its receptors (VEGFR1, VEGFR2 and VEGFR3) are important players in the development of this process. Binding of the ligand VEGF-A to VEGFR-2 triggers a signaling cascade leading to endothelial cell proliferation, migration, new vessel formation, and sustained angiogenesis[24]. Therefore, inhibition of the VEGF signaling has become a useful clinical maneuver in the treatment of several types of cancer.

**Anti-VEGF moAb:** Bevacizumab is a fully human moAb targeting VEGF-A[36]. The potential role of this drug in the management of patients with metastatic GC was evaluated in the phase Ⅲ AVAGAST and AVATAR trials. The AVAGAST trial was global, randomized, placebo-controlled trial conducted for evaluation of the benefits of bevacizumab when added to first-line capecitabine and cisplatin chemotherapy in 774 metastatic GC patients[37]. The trial did not show any significant improvement in OS in the bevacizumab cohort. Median OS was 12.1 mo with bevacizumab plus chemotherapy and 10.1 mo with placebo plus chemotherapy (HR = 0.87; 95%CI: 0.73 to 1.03; *P* = 0.1002). Despite this, both median PFS (6.7 mo *vs* 5.3 mo; HR = 0.80; 95%CI: 0.68 to 0.93; *P* = 0.0037) and overall response rate (46.0% *vs* 37.4%; *P* = 0.0315) were significantly increased by the addition of bevacizumab *vs* placebo. Preplanned subgroup analysis

of the study also demonstrated geographical differences in the therapeutic effectiveness of bevacizumab treatment. A survival benefit for bevacizumab was demonstrated in patients recruited from North America and Latin America centers (median, 11.5 mo *vs* 6.8 mo for placebo-chemotherapy; HR = 0.63; 95%CI: 0.43 to 0.94), whereas patients recruited from Asia centers seemed to have no obvious benefit (HR = 0.97; 95%CI: 0.75 to 1.25). Subsequently, the study investigators identified plasma VEGF-A levels and degree of tumor neuropilin-1, a co-receptor for VEGF-A, expression as potential predictive biomarkers of bevacizumab efficacy[38]. A negative OS correlation was found in patients with low expression of tumor neuropilin-1 (HR = 0.75; 95%CI: 0.59 to 0.97) compared to those with high expression (HR = 1.07; 95%CI: 0.81 to 1.40; interaction $P = 0.06$). Of note, these findings were significant only in non-Asian patients.

AVATAR, a study similar in design to AVAGAST, was performed in Chinese patient population with advanced GC[39]. It was again demonstrated that the addition of bevacizumab to chemotherapy consisting capecitabine and cisplatin in this specific patient population did not improve OS (11.4 mo in the placebo arm *vs* 10.5 mo in the bevacizumab arm, HR = 1.11; $P = 0.55$).

Ramucirumab is a novel humanized IgG1 moAb that selectively binds to the extracellular ligand binding domain of VEGFR-2 and blocks VEGF-induced angiogenic signaling[40]. In theory, this has the advantage of blocking signaling from VEGF isoforms other than VEGF-A. Its efficacy and safety in advanced GC was evaluated in two international, phase Ⅲ, randomized, double-blinded and placebo-controlled studies. In the REGARD trial, a total 355 advanced gastric or GEJ cancer patients progressing after first-line platinum- or fluoropyrimidine-based combination chemotherapy were randomized to receive best supportive care (BSC) plus either ramucirumab or placebo[41]. Ramucirumab was given intravenously every 2 wk at 8 mg/kg and the median treatment duration was 8 wk. Patients receiving ramucirumab had a significantly improved median OS (5.2 mo *vs* 3.8 mo; HR = 0.776; $P = 0.0473$) and PFS (2.1 mo *vs* 1.3 mo; HR = 0.483; $P < 0.0001$) than patients receiving placebo. The 12-wk PFS rate was 40% for ramucirumab group and 16% for placebo group. Additionally, the overall response rate (3.4% *vs* 2.6%) and disease control rate (49% *vs* 23%) were also higher in the ramucirumab group compared to the placebo group ($P < 0.0001$). Ramucirumab had an acceptable toxicity profile. The most frequently recorded grade 3 or higher side effects in patients receiving ramucirumab were hypertension, anemia, abdominal pain, ascites, fatigue and hyponatremia. After presentation of these results, ramucirumab was approved for the second-line therapy advanced GC in the United States. Interestingly, these results are quite similar to those achieved with chemotherapy in the second-line setting[42].

The RAINBOW study tested ramucirumab in combination with paclitaxel in metastatic GEJ or gastric adenocarcinoma patients who experienced disease progression after first-line platinum- and fluoropyrimidine-based chemotherapy[43]. In this study, 665 patients were randomly assigned to receive ramucirumab or placebo plus paclitaxel. OS was defined again primary endpoint for efficacy. Median OS for patients received ramucirumab plus paclitaxel was 9.6 mo, compared to 7.4 mo for those received paclitaxel alone (HR = 0.807; 95%CI: 0.678-0.962; $P = 0.0169$). Median PFS was 4.4 mo and 2.9 mo, respectively (HR = 0.635; 95%CI: 0.536-0.752; $P < 0.0001$). The objective response rate was higher in the combination arm compared to paclitaxel alone arm (28% *vs* 16%, $P = 0.0001$). Ramucirumab was relatively well tolerated. As expected, grade 3 or higher side effects were somewhat more frequent among patients receiving ramucirumab plus paclitaxel greater with combination treatment and included neutropenia, leukopenia, hypertension and fatigue. The RAINBOW study showed that an effective second-line treatment may improve the duration of survival in metastatic GC, and it is the only study to date to demonstrate a 2-mo improvement in OS in this setting. Therefore, ramucirumab is the first anti-angiogenic agent to demonstrate activity for advanced GC, and now approved both as monotherapy and in combination with paclitaxel for this malignancy.

**Anti-VEGF TKI:** Apatinib is an orally administered TKI that selectively binds to VEGFR-2 and inhibits VEGF-induced endothelial cell proliferation and migration. As a result, it leads to a significant decrease in tumor microvessel density[44]. In a phase II trial conducted in China, apatinib was shown to increase PFS and OS in patients with metastatic GC progressing after 2 or more previous lines of chemotherapy[45]. Data from a phase Ⅲ trial presented at the 2014 ASCO Annual Meeting confirmed the effectiveness of apatinib in this setting[46]. This trial included 273 patients with advanced GC who experienced disease progression after second-line treatment. Patients were randomly assigned to receive apatinib or placebo. The primary endpoint, median OS, was significantly longer in the apatinib group than in the placebo group (195 d *vs* 140 d; HR = 0.71; 95%CI: 0.54-0.94; $P < 0.016$). The apatinib group also had a better median PFS than the placebo group; 78 d *vs* 53 d, respectively (HR = 0.44; 95%CI: 0.33-0.61; $P < 0.0001$). Therefore, apatinib provides a new promising treatment option for advanced GC, although one which overlaps with ramucirumab in both degree of activity and mechanism.

Two multi-targeted kinase inhibitors that share VEGF receptors as targets are sunitinib and sorafenib. Both of these agents have been tested in GC and have shown some signs of efficacy, but have not progressed to advanced trials[47-49]. Given the modest activity and the toxicity profiles of these two agents, it is unlikely that they would supplant ramucirumab at this time and are no longer being studied in GC.

**The mTOR pathway:** The mTOR (mammalian target of rapamycin) is an essential cellular signaling pathway that has a crucial role in the regulation of cell growth, survival, proliferation, metabolism, and angiogenesis[50]. Everolimus, an orally administered rapamycin analog, is the only mTOR inhibitor that has been evaluated in advanced GC[51]. Phase Ⅱ trials documented that it can produce stabile disease in a significant portion of patients with chemo-refractory advanced GC. Despite these promising data, in the phase Ⅲ GRANITE-1 trial, everolimus failed to demonstrate any significant improvement in OS compared to BSC alone[52]. In this study, advanced GC patients who had progressive disease after first- or second-line cytotoxic chemotherapy were randomized to receive everolimus treatment (10 mg/d) or matching placebo in conjunction with BSC. Median OS was 5.4 mo for patients receiving everolimus and 4.3 mo for patients receiving placebo (HR = 0.90; 95%CI: 0.75 to 1.08; *P* = 0.124). Another phase Ⅲ trial (AIO-STO-0111) is now investigating the efficacy of everolimus when given in combination with paclitaxel in GC patients progressing following prior chemotherapy regimen.

### *Targeting the hepatocyte growth factor/c-MET signaling pathway*

A transmembrane protein-tyrosine kinase receptor c-MET and its ligand, hepatocyte growth factor (HGF) control many vital cellular events such as cell proliferation, survival, motility, invasion and angiogenesis[53]. C-MET overexpression has been detected in 18%-82% of GC patients, with genetic amplification of the CMET occurring in only 2%-3% of cases[54]. Patients with c-Met overexpressing tumors may have poorer survival, and the prognostic effect of overexpression seems to be independent of disease stage[53]. Therefore, c-MET has been recognized as potentially significant therapeutic target in GC.

Rilotumumab is a fully humanized IgG2 moAb that selectively binds HGF and prevents its binding to the MET receptor[53]. The results of a phase Ib/Ⅱ study of rilotumumab in combination with platinum-based chemotherapy in patients with locally advanced or metastatic GC have demonstrated the potential therapeutic value of drugs that target the c-MET pathway in this disease[55]. In the phase Ⅱ part of this study, 121 patients were randomized to ECX regimen plus placebo (*n* = 39) or ECX plus either 7.5 mg/kg (*n* = 42) or 15 mg/kg (*n* = 40) rilotumumab. Median PFS was 5.1 mo (2.9-7.0) in the rilotumumab 15 mg/kg group, 6.8 mo (4.5-7.5) in the rilotumumab 7.5 mg/kg group, 5.7 mo (4.5-7.0) in both rilotumumab groups combined, and 4.2 mo (2.9-4.9) in the placebo group. The HR for PFS compared with placebo was 0.69 (80%CI: 0.49-0.97; *P* = 0.164) for rilotumumab 15 mg/kg, 0.53 (80%CI: 0.38-0.73; *P* = 0.009) for rilotumumab 7.5 mg/kg, and 0.60 (80%CI: 0.45-0.79; *P* = 0.016) for combined rilotumumab. Rilotumumab was generally well tolerated by patients, with common side effects including neutropenia, anemia, thrombocytopenia, peripheral edema, and deep vein thrombosis. The association between MET expression and clinical outcomes was also evaluated in this trial. MET expression was found to be prognostic for shortened OS in the placebo group (5.7 mo *vs* 11.5 mo). In the subgroup of patients with increased MET expression, median OS was longer in patients receiving rilotumumab than in those receiving placebo (10.6 mo *vs* 5.7 mo). However, no survival benefit was seen with the addition of rilotumumab to chemotherapy among MET-negative patients.

Based on these data, the RILOMET-1 [a multicenter, randomized, double-blind, placebo-controlled phase Ⅲ study of rilotumumab (15 mg/kg) plus ECX regimen as first-line therapy for metastatic MET-positive gastric or GEJ adenocarcinoma] and the RILOMET-2 trial (a multicenter, randomized, double-blind, placebo controlled phase Ⅲ study of rilotumumab plus cisplatin and capecitabine regimen as first-line therapy for Asian patients with metastatic MET-positive gastric or GEJ cancer) have been conducted. Unfortunately, the RILOMET-1 study has been reported as negative via press release (AMGEN press release), with final presentation of data pending at an upcoming meeting.

Onartuzumab is an Escherichia coli-derived humanized monovalent moAb against MET that specifically binds to the MET receptor and blocks HGF-MET binding[56]. Shah *et al*[57] have presented the results of a phase II trial that compared FOLFOX plus onartuzumab *vs* FOLFOX plus placebo in patients with metastatic gastroesophageal adenocarcinoma. The primary endpoint of the trial was not met (6.77 mo in onartuzumab arm *vs* 6.97 mo in the placebo arm, HR = 1.08; 95%CI: 0.71-1.63). In MET-positive patients, PFS was 5.95 mo for patients receiving onartuzumab *vs* 6.8 mo for those in the placebo arm (HR = 1.38; 95%CI: 0.60-3.20). Serious adverse events, including neutropenia, thrombocytopenia, peripheral edema, and pulmonary embolism also occurred more frequently in patients on onartuzumab (55% *vs* 40%).

The phase Ⅲ MetGastric trial will assess the effectiveness and toxicity of onartuzumab in combination with modified-FOLFOX6 chemotherapy in patients with metastatic HER2-negative and MET-positive gastric or GEJ adenocarcinoma[58]. In this study, enrolled patients will receive the chemotherapy with either onartuzumab or placebo, and patients who have not progressed after 12 cycles of treatment will continue with either onartuzumab or placebo until evidence of disease progression or intolerable toxicity.

### *Targeting programmed cell death-1 receptor and its ligand*

Programmed cell death-1 (PD-1) is a cell surface and immune inhibitory receptor expressed on a variety of immune cells, especially cytotoxic T cells. Two distinct ligands for PD-1 were identified: Programmed death ligand 1 (PD-L1) and PD-L2[59]. While PD-L2 is expressed mainly on macrophages and dendritic cells, PDL-1 is expressed exclusively by tumor cells and their

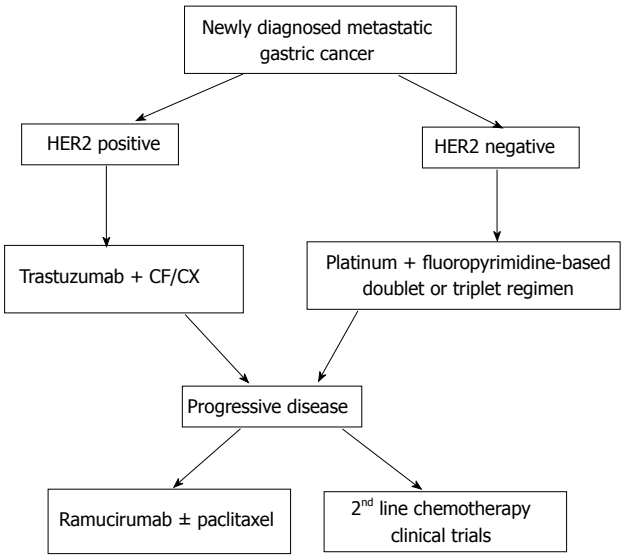


**Figure 2 Proposed targeted therapy algorithm for advanced gastric cancer.** CF: Cisplatin plus 5-Fluorouracil; HER: Human epidermal growth factor receptor; CX: Cisplatin plus capecitabine.

microenvironment[60]. Tumors that express PD-L1 often tend to be aggressive and carry a poor prognosis[61]. Tumor cells utilize the PD-1/PD-L1 pathway to evade immune-cell attack. Activation of this pathway in tumor cells blocks T-cell-mediated cytotoxicity and allows tumor cells to continue to proliferate[59-61]. Drugs targeting PD-L1 pathway may stimulate antitumor immunity, especially (although not exclusively) in PD-L1 positive tumors.

At the 2014 European Society for Medical Oncology meeting, data on safety and tolerability, and preliminary anti-tumor efficacy of pembrolizumab in advanced GC patients were presented by Muro *et al*[62] (KEYNOTE-012 study). This drug is a selective and humanized moAb that blocks interaction between PD-1 and its ligands PD-L1 and PD-L2. Muro *et al*[62] enrolled 39 patients with PD-L1 positive advanced GC: 19 from Asia-Pacific, 20 from rest of world. Sixty-seven percent of these patients had received more than 2 chemotherapy lines. Pembrolizumab was administered 10 mg/kg once every 2 wk for up to 24 mo in the absence of intolerable toxicity or disease progression. The overall response rate was 31.6% in patients in the Asia-Pacific region and 30% in patients from rest the world. Median duration of response has not yet been reached at the time of initial presentation, but ranged from 8+ to 20+ wk. Four patients developed grade 3-5 drug-related adverse events including peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis ($n$ = 1 each). One treatment-related death was recorded due to hypoxia. The authors of the study have concluded that pembrolizumab treatment seems to have and acceptable safety and tolerability profile and it provides encouraging clinical antitumor activity in chemo-refractory disease. On the basis of these promising preliminary data, phase II KEYNOTE-059 study will be initiated to evaluate pembrolizumab as single agent or in combination with cisplatin and 5-FU in patients with metastatic PD-L1 positive gastric or GEJ adenocarcinoma.

**Recent analysis from the Gastric Cancer Genome Atlas Project:** The Cancer Genome Atlas is a large-scale effort coordinated by the United States National Cancer Institute to extensively characterize the genetic and epigenetic landscape of human cancers. The group has reported on the analysis of 259 untreated primary gastric cancers. This analysis proposed dividing gastric cancer into 4 molecular subtypes: EBV driven, microsatellite unstable (MSI high), genomic stable and chromosomal unstable tumors. This molecular subtyping highlights important targets within these groups for further study, and potentially allows for patient enrichment that could result in higher chance of positive trial results. For example, EBV driven tumors are characterized by high rate of PIK3CA mutations, where drugs targeting the Pi3K pathway are available in clinical trials[63]. Additionally, EBV-positive gastric cancers preferentially overexpress CD274 and PDCD1LG2 (PD-L1 and PD-L2) that were discussed above[64]. These are currently being evaluated as predictive biomarkers for immune checkpoint inhibitor activity[65,66]. In addition, this subgroup has significant promoter hypermethylation, such that evaluating hypomethylating agents such as azacitidine, decitabine and others in clinical development might represent a promising strategy.

The MSI-high genotype is associated with high mutational rate, representing a wealth of antigens that could be recognized by the immune system[67,68]. This genotype has been proposed to be responsive to checkpoint inhibitors, and clinical trials are ongoing (NCT01876511, NCT02060188) addressing response to checkpoint inhibitors in MSI high gastrointestinal cancers.

Other mutations that have been reported (KRAS, P53, APC, and CTNNB1) are still challenging to target and are the subject of numerous reviews. Knowledge of frequency of mutation of these genes, however, provides impetus for further basic research. For example, cell cycle regulators could have better chance of activity in P53 mutant tumors[69,70]. Lastly, the WNT/beta catenin pathway is currently a focus of much preclinical and clinical research[71].

## CONCLUSION

Gastric cancer has long represented one of the most difficult gastrointestinal malignancies to treat. Encouragingly, recent progress with targeted therapies offers hope for patients with advanced GC, and expands the therapeutic armamentarium considerably against this formidable disease. As these therapies continue to be developed, we must focus on determination of predictive markers, and preferably co-develop drugs with these markers. The mechanisms underlying primary or acquired resistance to targeted agents also should be clarified in order to help further drug development.

We propose a treatment algorithm that is consistent with current National Cancer Center Network guidelines (version 3, 2015) and that integrates targeted therapies into the management of advanced GC (Figure 2). The addition of trastuzumab to a first-line chemotherapy doublet (cisplatin and capecitabine or 5-FU) is now considered standard of care for patients with HER2 positive advanced GC. The results of the phase III JACOB trial are awaited with great interest to see if the combined use of trastuzumab and pertuzumab can improve clinical outcome. Anti-angiogenic therapy has failed to meet the expectations as first-line treatment. But second-line treatment with ramucirumab or apatinib now represents a good alternative for chemo-refractory GC patients for whom the options are still are quite limited. Other targeted agents currently under evaluation in clinical trials including inhibitors of m-TOR, c-MET, IGFR, and FGFR pathways can help expand our treatment repertoire in the future against advanced GC. Lastly, knowledge gained from detailed molecular profiling of gastric cancers gives us a roadmap for future basic and clinical research.

## REFERENCES


1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

2 **De Vita F**, Di Martino N, Fabozzi A, Laterza MM, Ventriglia J, Savastano B, Petrillo A, Gambardella V, Sforza V, Marano L, Auricchio A, Galizia G, Ciardiello F, Orditura M. Clinical management of advanced gastric cancer: the role of new molecular drugs. *World J Gastroenterol* 2014; **20**: 14537-14558 [PMID: 25356019 DOI: 10.3748/wjg.v20.i40.14537]

3 **Meyerhardt JA**, Fuchs CS. Adjuvant therapy in gastric cancer: can we prevent recurrences? *Oncology* (Williston Park) 2003; **17**: 714-721, 728; discussion 728-729, 732-733 [PMID: 12800796]

4 **Kanat O**, O'Neil BH. Metastatic gastric cancer treatment: a little slow but worthy progress. *Med Oncol* 2013; **30**: 464 [PMID: 23335104 DOI: 10.1007/s12032-013-0464-4]

5 **Wagner AD**, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930]

6 **Oba K**, Paoletti X, Bang YJ, Bleiberg H, Burzykowski T, Fuse N, Michiels S, Morita S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Shitara K, Tsuburaya A, Van Cutsem E, Buyse M. Role of chemotherapy for advanced/recurrent gastric cancer: an individual-patient-data meta-analysis. *Eur J Cancer* 2013; **49**: 1565-1577 [PMID: 23352439 DOI: 10.1016/j.ejca.2012.12.016]

7 **Schinzari G**, Cassano A, Orlandi A, Basso M, Barone C. Targeted therapy in advanced gastric carcinoma: the future is beginning. *Curr Med Chem* 2014; **21**: 1026-1038 [PMID: 24304282]

8 **Catalano V**, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. *Crit Rev Oncol Hematol* 2009; **71**: 127-164 [PMID: 19230702 DOI: 10.1016/j.critrevonc.2009.01.004]

9 **Lordick F**, Allum W, Carneiro F, Mitry E, Tabernero J, Tan P, Van Cutsem E, van de Velde C, Cervantes A. Unmet needs and challenges in gastric cancer: the way forward. *Cancer Treat Rev* 2014; **40**: 692-700 [PMID: 24656602 DOI: 10.1016/j.ctrv.2014.03.002]

10 **Yang W**, Raufi A, Klempner SJ. Targeted therapy for gastric cancer: molecular pathways and ongoing investigations. *Biochim Biophys Acta* 2014; **1846**: 232-237 [PMID: 24858418 DOI: 10.1016/j.bbcan.2014.05.003]

11 **Zagouri F**, Papadimitriou CA, Dimopoulos MA, Pectasides D. Molecularly targeted therapies in unresectable-metastatic gastric cancer: a systematic review. *Cancer Treat Rev* 2011; **37**: 599-610 [PMID: 21676549 DOI: 10.1016/j.ctrv.2011.03.007]

12 **Kasper S**, Schuler M. Targeted therapies in gastroesophageal cancer. *Eur J Cancer* 2014; **50**: 1247-1258 [PMID: 24495747 DOI: 10.1016/j.ejca.2014.01.009]

13 **Martinelli E**, De Palma R, Orditura M, De Vita F, Ciardiello F. Anti-epidermal growth factor receptor monoclonal antibodies in cancer therapy. *Clin Exp Immunol* 2009; **158**: 1-9 [PMID: 19737224 DOI: 10.1111/j.1365-2249.2009.03992.x]

14 **Normanno N**, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, Carotenuto A, De Feo G, Caponigro F, Salomon DS. Epidermal growth factor receptor (EGFR) signaling in cancer. *Gene* 2006; **366**: 2-16 [PMID: 16377102]

15 **Tomas A**, Futter CE, Eden ER. EGF receptor trafficking: consequences for signaling and cancer. *Trends Cell Biol* 2014; **24**: 26-34 [PMID: 24295852 DOI: 10.1016/j.tcb.2013.11.002]

16 **Marshall J**. Clinical implications of the mechanism of epidermal growth factor receptor inhibitors. *Cancer* 2006; **107**: 1207-1218 [PMID: 16909423]

17 **Wong H**, Yau T. Targeted therapy in the management of advanced gastric cancer: are we making progress in the era of personalized medicine? *Oncologist* 2012; **17**: 346-358 [PMID: 22334453 DOI: 10.1634/theoncologist.2011-0311]

18 **Meza-Junco J**, Sawyer MB. Metastatic gastric cancer - focus on targeted therapies. *Biologics* 2012; **6**: 137-146 [PMID: 22807624 DOI: 10.2147/BTT.S23917]

19 **Smyth EC**, Cunningham D. Targeted therapy for gastric cancer. *Curr Treat Options Oncol* 2012; **13**: 377-389 [PMID: 22552927 DOI: 10.1007/s11864-012-0192-6]

20 **Cidon EU**, Ellis SG, Inam Y, Adeleke S, Zarif S, Geldart T. Molecular targeted agents for gastric cancer: a step forward towards personalized therapy. *Cancers* (Basel) 2013; **5**: 64-91 [PMID: 24216699 DOI: 10.3390/cancers5010064]

21 **Enzinger PC**, Burtness B, Hollis D, Niedzwiecki D, Ilson D, Benson AB, Mayer RJ, Goldberg RM. CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. *J Clin Oncol* 2010; **28**: 15

22 **Lordick F**, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499 [PMID: 23594786 DOI: 10.1016/S1470-2045(13)70102-5]

23 **Waddell T**, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadsley J, Ferry D, Mansoor W, Crosby T, Coxon F, Smith D, Waters J, Iveson T, Falk S, Slater S, Peckitt C, Barbachano Y. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 481-489 [PMID: 23594787 DOI: 10.1016/S1470-2045(13)70096-2]

24 **Shum H**, Rajdev L. Multimodality management of resectable gastric cancer: A review. *World J Gastrointest Oncol* 2014; **6**: 393-402 [PMID: 25320655 DOI: 10.4251/wjgo.v6.i10.393]

25 **Rao S**, Starling N, Cunningham D, Sumpter K, Gilligan D, Ruhstaller T, Valladares-Ayerbes M, Wilke H, Archer C, Kurek R, Beadman C, Oates J. Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study. *Ann Oncol* 2010; **21**: 2213-2219 [PMID: 20497967 DOI: 10.1093/annonc/mdq247]

26 **Satoh T**, Lee KH, Rha SY, Sasaki Y, Park SH, Komatsu Y, Yasui H, Kim TY, Yamaguchi K, Fuse N, Yamada Y, Ura T, Kim SY,

Munakata M, Saitoh S, Nishio K, Morita S, Yamamoto E, Zhang Q, Kim JM, Kim YH, Sakata Y. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. *Gastric Cancer* 2015; **18**: 824-832 [PMID: 25185971]

27 **Dragovich T**, Campen C. Anti-EGFR-Targeted Therapy for Esophageal and Gastric Cancers: An Evolving Concept. *J Oncol* 2009; **2009**: 804108 [PMID: 19636422 DOI: 10.1155/2009/804108]

28 **Wainberg ZA**, Lin LS, DiCarlo B, Dao KM, Patel R, Park DJ, Wang HJ, Elashoff R, Ryba N, Hecht JR. Phase II trial of modified FOLFOX6 and erlotinib in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. *Br J Cancer* 2011; **105**: 760-765 [PMID: 21811258 DOI: 10.1038/bjc.2011.280]

29 **Chua TC**, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. *Int J Cancer* 2012; **130**: 2845-2856 [PMID: 21780108 DOI: 10.1002/ijc.26292]

30 **Morishita A**, Gong J, Masaki T. Targeting receptor tyrosine kinases in gastric cancer. *World J Gastroenterol* 2014; **20**: 4536-4545 [PMID: 24782606 DOI: 10.3748/wjg.v20.i16.4536]

31 **Won E**, Janjigian YJ, Ilson DH. HER2 directed therapy for gastric/esophageal cancers. *Curr Treat Options Oncol* 2014; **15**: 395-404 [PMID: 24811128 DOI: 10.1007/s11864-014-0292-6]

32 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736[10)61121-X]

33 **Barok M**, Joensuu H, Isola J. Trastuzumab emtansine: mechanisms of action and drug resistance. *Breast Cancer Res* 2014; **16**: 209 [PMID: 24887180 DOI: 10.1186/bcr3621]

34 **Hecht JR**, Bang YJ, Qin S, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero AF, Salman P, Li J, Protsenko S, Buyse ME, Afenjar K, Kaneko T, Kemner A, Santillana S, Press MF, Slamon DJ. Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial. *J Clin Oncol* 2013; **31**: LBA4001

35 **Bang YJ**. A randomized, open-label, phase III study of lapatinib in combination with weekly paclitaxel versus weekly paclitaxel alone in the second-line treatment of HER2 amplified advanced gastric cancer (AGC) in Asian population: Tytan study. *J Clin Oncol* 2013; **31**: 11

36 **O'Neil BH**, McCarthy T. Angiogenesis inhibitors in gastric cancer. *Orphan Drugs: Research and Reviews* 2014; **4**: 55-61

37 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236]

38 **Van Cutsem E**, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, Peng Yong W, Langer B, Delmar P, Scherer SJ, Shah MA. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30**: 2119-2127 [PMID: 22565005 DOI: 10.1200/JCO.2011.39.9824]

39 **Shen L**, Li J, Xu J, Pan H, Dai G, Qin S, Wang L, Wang J, Yang Z, Shu Y, Xu R, Chen L, Liu Y, Yu S, Bu L, Piao Y. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 2015; **18**: 168-176 [PMID: 24557418 DOI: 10.1007/s10120-014-0351-5]

40 **Fontanella C**, Ongaro E, Bolzonello S, Guardascione M, Fasola G, Aprile G. Clinical advances in the development of novel VEGFR2 inhibitors. *Ann Transl Med* 2014; **2**: 123 [PMID: 25568876 DOI: 10.3978/j.issn.2305-5839.2014.08.14]

41 **Fuchs CS**, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31-39 [PMID: 24094768 DOI: 10.1016/S0140-6736(13)61719-5]

42 **Ford HE**, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, Swinson D, Falk S, Chau I, Cunningham D, Kareclas P, Cook N, Blazeby JM, Dunn JA. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014; **15**: 78-86 [PMID: 24332238 DOI: 10.1016/S1470-2045(13)70549-7]

43 **Wilke H**, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1224-1235 [PMID: 25240821 DOI: 10.1016/S1470-2045(14)70420-6]

44 **Geng R**, Li J. Apatinib for the treatment of gastric cancer. *Expert Opin Pharmacother* 2015; **16**: 117-122 [PMID: 25420417 DOI: 10.1517/14656566.2015.981526]

45 **Li J**, Qin S, Xu J, Guo W, Xiong J, Bai Y, Sun G, Yang Y, Wang L, Xu N, Cheng Y, Wang Z, Zheng L, Tao M, Zhu X, Ji D, Liu X, Yu H. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol* 2013; **31**: 3219-3225 [PMID: 23918952 DOI: 10.1200/JCO.2013.48.8585]

46 **Qin S**. Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2014; **32**: 5

47 **Bang YJ**, Kang YK, Kang WK, Boku N, Chung HC, Chen JS, Doi T, Sun Y, Shen L, Qin S, Ng WT, Tursi JM, Lechuga MJ, Lu DR, Ruiz-Garcia A, Sobrero A. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs* 2011; **29**: 1449-1458 [PMID: 20461441 DOI: 10.1007/s10637-010-9438-y]

48 **Yi JH**, Lee J, Lee J, Park SH, Park JO, Yim DS, Park YS, Lim HY, Kang WK. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. *Br J Cancer* 2012; **106**: 1469-1474 [PMID: 22460270 DOI: 10.1038/bjc.2012.100]

49 **Sun W**, Powell M, O'Dwyer PJ, Catalano P, Ansari RH, Benson AB. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. *J Clin Oncol* 2010; **28**: 2947-2951 [PMID: 20458043 DOI: 10.1200/JCO.2009.27.7988]

50 **Bjornsti MA**, Houghton PJ. The TOR pathway: a target for cancer therapy. *Nat Rev Cancer* 2004; **4**: 335-348 [PMID: 15122205]

51 **Doi T**, Muro K, Boku N, Yamada Y, Nishina T, Takiuchi H, Komatsu Y, Hamamoto Y, Ohno N, Fujita Y, Robson M, Ohtsu A. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. *J Clin Oncol* 2010; **28**: 1904-1910 [PMID: 20231677 DOI: 10.1200/JCO.2009.26.2923]

52 **Ohtsu A**, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935-3943 [PMID: 24043745 DOI: 10.1200/JCO.2012.48.3552]

53 **Hack SP**, Bruey JM, Koeppen H. HGF/MET-directed therapeutics in gastroesophageal cancer: a review of clinical and biomarker development. *Oncotarget* 2014; **5**: 2866-2880 [PMID: 24930887]

54 **Sotoudeh K**, Hashemi F, Madjd Z, Sadeghipour A, Molanaei S, Kalantary E. The clinicopathologic association of c-MET overexpression in Iranian gastric carcinomas; an immunohistochemical study of tissue microarrays. *Diagn Pathol* 2012; **7**: 57 [PMID: 22640970 DOI: 10.1186/1746-1596-7-57]

55 **Iveson T**, Donehower RC, Davidenko I, Tjulandin S, Deptala A, Harrison M, Nirni S, Lakshmaiah K, Thomas A, Jiang Y, Zhu M, Tang R, Anderson A, Dubey S, Oliner KS, Loh E. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. *Lancet Oncol* 2014; **15**: 1007-1018 [PMID: 24965569 DOI: 10.1016/S1470-2045(14)70023-3]

56 **Merchant M**, Ma X, Maun HR, Zheng Z, Peng J, Romero M, Huang A, Yang NY, Nishimura M, Greve J, Santell L, Zhang YW, Su Y, Kaufman DW, Billeci KL, Mai E, Moffat B, Lim A, Duenas ET, Phillips HS, Xiang H, Young JC, Vande Woude GF, Dennis MS, Reilly DE, Schwall RH, Starovasnik MA, Lazarus RA, Yansura DG. Monovalent antibody design and mechanism of action of onartuzumab, a MET antagonist with anti-tumor activity as a therapeutic agent. *Proc Natl Acad Sci USA* 2013; **110**: E2987-E2996 [PMID: 23882082 DOI: 10.1073/pnas.1302725110]

57 **Shah MA**, Cho JY, Huat ITB, Tebbutt NC, Yen CJ, Kang A, Shames DS, Bu L, Kang YK. Randomized phase II study of FOLFOX /- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC). *J Clin Oncol* 2015; **33**: 2

58 **Cunningham D**, Bang YJ, Tabernero J, Shah MA, Lordick F, Hack SP. MetGastric: A randomized phase III study of onartuzumab (MetMAb) in combination with mFOLFOX6 in patients with metastatic HER2-negative and MET-positive adenocarcinoma of the stomach or gastroesophageal junction. *J Clin Oncol* 2015; **33**: TPS4155

59 **Momtaz P**, Postow MA. Immunologic checkpoints in cancer therapy: focus on the programmed death-1 (PD-1) receptor pathway. *Pharmgenomics Pers Med* 2014; **7**: 357-365 [PMID: 25484597 DOI: 10.2147/PGPM.S53163.]

60 **Kim JW**, Eder JP. Prospects for targeting PD-1 and PD-L1 in various tumor types. *Oncology* (Williston Park) 2014; **28** Suppl 3: 15-28 [PMID: 25387682]

61 **Dolan DE**, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. *Cancer Control* 2014; **21**: 231-237 [PMID: 24955707]

62 **Muro K**, Bang Y, Shankaran V, Geva R, Catenacci DVT, Gupta S, Eder JP, Berger R, Gonzalez EJ, Pulini J, Ray AB, Dolled-Filhart M, Emancipator K, Pathiraja K, Shu X, Koshiji MR, Cheng JD, Chung HC. LBA15 - A phase 1b study of pembrolizumab (Pembro; MK-3475) in patients (Pts) with advanced gastric cancer. *Ann Oncol* 2014; **25**: 1-41

63 **Courtney KD**, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. *J Clin Oncol* 2010; **28**: 1075-1083 [PMID: 20085938 DOI: 10.1200/JCO.2009.25.3641]

64 **Gulley ML**. Genomic assays for Epstein-Barr virus-positive gastric adenocarcinoma. *Exp Mol Med* 2015; **47**: e134 [PMID: 25613731 DOI: 10.1038/emm.2014.93]

65 **Herbst RS**, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**: 563-567 [PMID: 25428504 DOI: 10.1038/nature14011]

66 **Patel SP**, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. *Mol Cancer Ther* 2015; **14**: 847-856 [PMID: 25695955 DOI: 10.1158/1535-7163.MCT-14-0983]

67 **Xiao Y**, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. *Cancer Discov* 2015; **5**: 16-18 [PMID: 25583798 DOI: 10.1158/2159-8290.CD-14-1397]

68 **Llosa NJ**, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, Blosser RL, Fan H, Wang H, Luber BS, Zhang M, Papadopoulos N, Kinzler KW, Vogelstein B, Sears CL, Anders RA, Pardoll DM, Housseau F. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov* 2015; **5**: 43-51 [PMID: 25358689 DOI: 10.1158/2159-8290]

69 **Hirai H**, Iwasawa Y, Okada M, Arai T, Nishibata T, Kobayashi M, Kimura T, Kaneko N, Ohtani J, Yamanaka K, Itadani H, Takahashi-Suzuki I, Fukasawa K, Oki H, Nambu T, Jiang J, Sakai T, Arakawa H, Sakamoto T, Sagara T, Yoshizumi T, Mizuarai S, Kotani H. Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. *Mol Cancer Ther* 2009; **8**: 2992-3000 [PMID: 19887545 DOI: 10.1158/1535-7163.MCT-09-0463]

70 **Rajeshkumar NV**, De Oliveira E, Ottenhof N, Watters J, Brooks D, Demuth T, Shumway SD, Mizuarai S, Hirai H, Maitra A, Hidalgo M. MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. *Clin Cancer Res* 2011; **17**: 2799-2806 [PMID: 21389100 DOI: 10.1158/1078-0432.CCR-10-2580]

71 **Madan B**, Virshup DM. Targeting Wnts at the source--new mechanisms, new biomarkers, new drugs. *Mol Cancer Ther* 2015; **14**: 1087-1094 [PMID: 25901018 DOI: 10.1158/1535-7163.MCT-14-1038]


**P- Reviewer**: Lee TY **S- Editor**: Qiu S **L- Editor**: A
**E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com